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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/684,209	10/10/2003	Se-Jin Lee	JHU1430-2	5214

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EXAMINER	
KEMMERER, ELIZABETH	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	**Application No.** 10/684,209	**Applicant(s)** LEE ET AL.	
	Examiner Elizabeth C. Kemmerer, Ph.D.	**Art Unit** 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-21 and 43-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-21 and 43-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The preliminary amendment filed 10 October 2003 and 05 April 2004 have been entered in full. Claims 1-14 and 22-42 are canceled. Claims 15-21 and 43-49 are under examination.

The information disclosure statement received 10 October 2003 has been considered.

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 15, it is unclear to what the phrase "or fragments thereof" refers: fragments of antibodies, or whole antibodies that bind fragments of the recited polypeptide. Claims 16-21 are included in this rejection since they depend from claim 15 without resolving the issue. Additionally, in claim 15, the method steps do not achieve the goal set forth in the preamble. The preamble is directed to detecting a cell proliferative disorder, whereas the method steps are directed to detecting the presence of Lefty-2 polypeptide in a sample, and mention Lefty-2 associated disorder. Therefore, it is not clear whether the claim is directed to a method of detecting a cell proliferative disorder, a Lefty-2 associated disorder, or merely the presence of Lefty-2 in a sample.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 15-21 are broadly directed to methods of detecting cell proliferative disorders comprising contacting an antibody that binds Lefty-2, or fragments thereof, with a specimen of a subject suspected of having a Lefty-2 associated disorder and detecting binding of the antibody. The specification discloses the structure of a new polynucleotide, Lefty-2, and the polypeptide encoded thereby. The specification discloses that Lefty-2 is a new member of the TGF-β family of proteins, and asserts that Lefty-2 would be expected to have cell growth and differentiation enhancing activities similar to other TGF-β family members. The specification also states that Lefty-2 may be involved in cell proliferative disorders.

Regarding the phrase "cell proliferative disorder," it is noted that there are disorders characterized by excessive cell proliferation (e.g., cancer, psoriasis) and disorders characterized by insufficient cell proliferation (e.g., neutropenia). Also, the type of cell is not limited in the claims. Regarding the phrase "Lefty-2 associated disorder," it is noted that the claims do not specify whether such a disorder is characterized by too much Lefty-2 or too little Lefty-2, or an alteration in the structure of Lefty-2, or an alteration in the timing of expression of Lefty-2. The claims also do not specify a structure for the recited Lefty-2.

Factors to be considered in determining whether a disclosure enables one skilled in the art to make and use the claimed invention in its full scope without resorting to undue experimentation include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature or complexity of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. See *In re Wands*, 8 USPQ2d. 1400 (Fed. Cir. 1988).

In the instant case, the quantity of experimentation required is quite large. A plethora of cell proliferative disorders exist, characterized by over-proliferation and under-proliferation, and involving any cell type. The amount of screening that would have to be done empirically to determine which disorders correlate with a change in amount, structure, or timing of expression of Lefty-2 is enormous. The specification provides no guidance regarding a nexus between alterations in Lefty-2 expression levels, structure, or timing of expression and any particular cell proliferative disorder, such that Lefty-2 can be used to diagnose any particular cell proliferative disorder. There are no working examples. The nature of the invention is very complex, involving disease states and altered protein amounts, structures, and/or timing of expression. The state of the prior art is silent with respect to a nexus between Lefty-2 and any cell proliferative disorder. There is no way to predict which cell proliferative disorder would involve Lefty-2 without empirical research. Finally, the breadth of the claims is quite large, reciting no limitations regarding the type of cell, whether proliferation is too high or too low, or the structure o the Lefty-2 protein.

Regarding the structure of the Lefty-2 proteins, the claims embrace muteins and variants of the single Lefty-2 polypeptide that is actually disclosed (i.e., human Lefty-2 of SEQ ID NO: 2). Such variants are also not enabled by the specification. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Finally, the specification fails to disclose an activity assay that is specific for Lefty-2, and thus it would be impossible for the skilled artisan to screen for active Lefty-2 variants. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 43-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods wherein the recited Lefty-2 protein consists of SEQ ID NO: 2, does not reasonably provide enablement for the claimed methods herein other Lefty-2 proteins are detected. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 43-49 are directed to methods of detecting Lefty-2 proteins in a sample using an antibody. The claims do not specify the structure of the recited Lefty-2 proteins, and thus encompass detection of Lefty-2 muteins and variants. As discussed above, the specification discloses a single Lefty-2 protein, namely, the human Lefty-2 protein of SEQ ID NO: 2. For the same reasons discussed above, the specification does not enable screening of Lefty-2 muteins and variants.

Conclusion

The claims are free of the art. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

ECK

ELIZABETH KEMMERER
PRIMARY EXAMINER